(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 December 2002 (19.12.2002)

PCT

(10) International Publication Number
WO 02/100878 A1

(51) International Patent Classification[7]: C07J 5/00, 3/00, 71/00

(21) International Application Number: PCT/GB02/02644

(22) International Filing Date: 11 June 2002 (11.06.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
102.628 12 June 2001 (12.06.2001) PT

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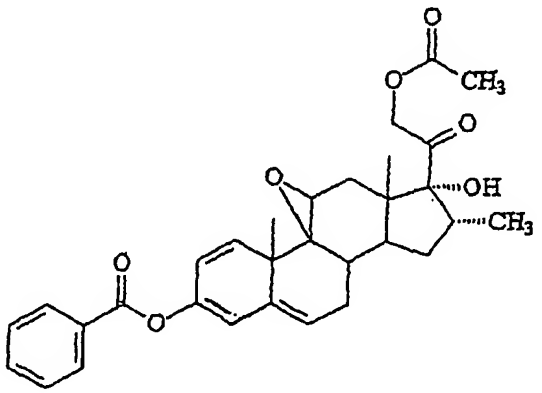
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PREPARATION OF FLUMETHASONE AND ITS 17-CARBOXYL ANDROSTEN ANALOGUE



(IIIa)

(57) Abstract: A process for preparing flumethasone (6a,9a-diffluoro-11β,17a,21-trihydroxy-16a-methyl-pregna-1,4-diene-3,20-dione), fulmethasone 21-acetate or its 17-carboxyl androsten analogue which process comprises reacting a compound of formula (IIIa) with an electrophilic fluorination agent.

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PREPARATION OF FLUMETHASONE AND ITS 17-CARBOXYL ANDROSTEN ANALOGUE

This invention relates to a process for preparing flumethasone, flumethasone 21-acetate and its 17-carboxyl androsten analogue, and to certain starting materials for the process.

Flumethasone, 6a,9a-difluoro-16a-methylprednisolone was described for the first time in 1962. Although this corticosteroid has an enhanced anti-inflammatory activity, it has not been widely used clinically. At the present time, its economical preparation on an industrial scale is ever more important because it is also an excellent starting material for the production of new difluoro-17-carboxyl androstenes, which are becoming increasingly important from a clinical point of view.

Flumethasone and its production are the subject of a number of patents including US 3,499,016 (1962) and British Patent 902,292 (1970). The new synthetic techniques developed since 1970 naturally permit a more efficient production of flumethasone with considerably increased yields compared to those obtained with the initial patents.

We have now devised a new process for the preparation of flumethasone as well as to the preparation of 6a,9a-difluoro-11ß,17a-dihydroxy-16a-methyl-17ß-carboxy-androsta-1,4-diene-3-one which is also called "hydroxyacid", an excellent starting material for the production of fluticasone and other new anti-inflammatory compounds of the androsta-1,4-diene series. The "hydroxyacid" was first described and claimed in US 3,636,010 (priority 1968).

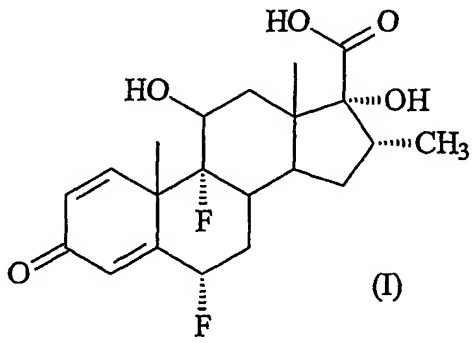
European Patent 0 610 138 131 (1994) describes a synthetic route for the preparation of the so called "hydroxyacid". However, the present invention represents considerable unexpected advantages in relation to this prior process patent, namely:

- the reaction sequence is reduced by one reaction step and by the elimination of the desolvatation step of 6a,9a-difluoro-11ß,17a-dihydroxy 16a-methyl 17ß-methoxycarbonyl androsta-1,4-diene-3-one, an additional production step,
- the present process avoids the use of a highly toxic reagent, dimethyl sulphate,

- permits the simultaneous deacetylation and degradative oxidation of the pregnane side chain forming directly the equivalent androstan derivative,
- increased yield of the hydroxyacid with excellent purity.

Whilst all the reaction steps of the present invention are realised in the pregnane series excepting the last one thus permitting an efficient preparation of flumethasone, the reaction sequence of EP 0 610 138 131 transforms the common starting material of both processes as from the first step into the androstane series.

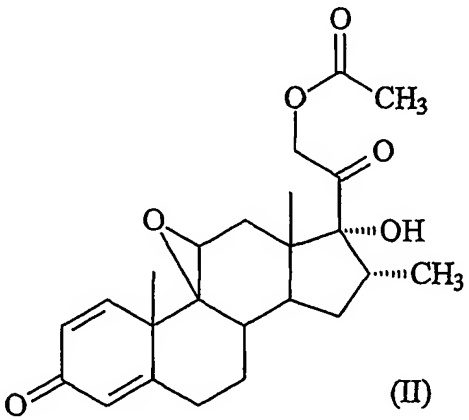
According to the present invention, there is provided a process for preparing flumethasone (6a,9a-difluoro-11ß,17a,21-trihydroxy-16a-methyl-pregna-1,4-diene-3,20-dione), fulmethasone 21-acetate or its 17-carboxyl androsten analogue of the formula:



(I)

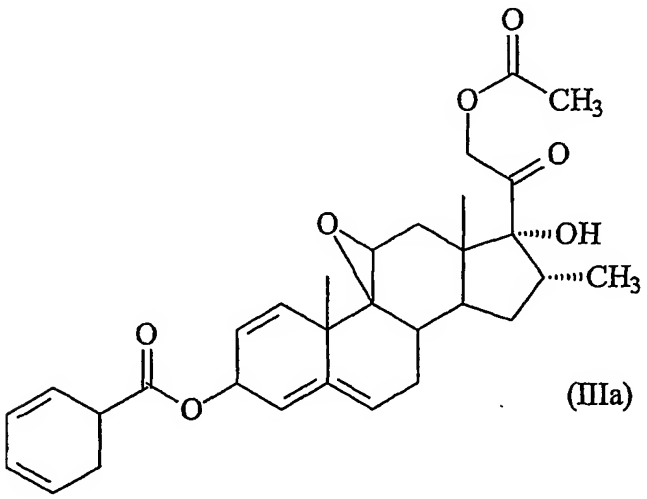
which process comprises

(a) reacting a compound of formula (II)



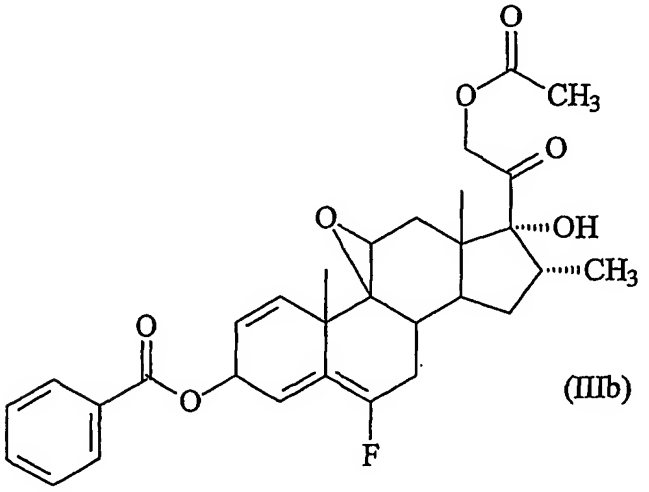
(II)

with benzoyl chloride to form a 3-enolic ester of the formula (IIIa):



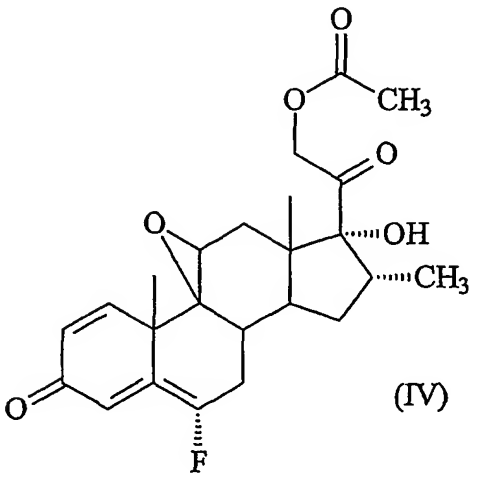
(IIIa)

b) reacting the enol benzoate (III a) with an electrophilic fluorination agent to introduce fluorine in the 6a- position to form a compound of formula (IIIb):



(IIIb)

(c) deprotecting the compound (IIIb) at C3 to form a compound of formula (IV):



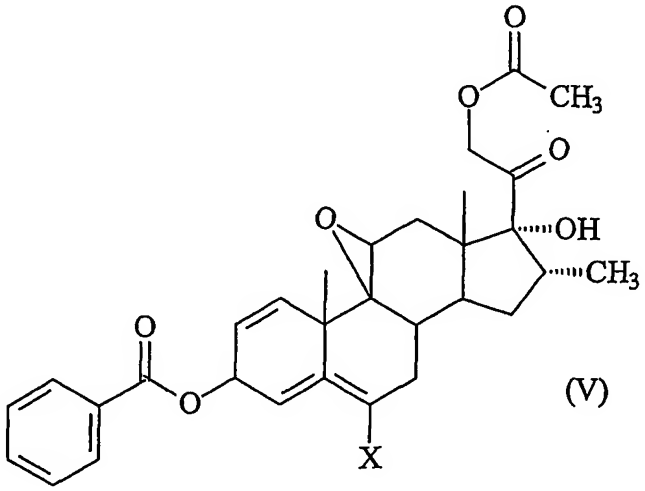
(IV)

(d) Fluorinating the 9,11-epoxy group of compound IV by reacting it with hydrofluoric acid to yield flumethasone 21-acetate; and

(e) optionally hydrolysing the flumethasone 21-acetate, in the presence or absence of an oxidation agent, to yield compound (I) or flumethasone, respectively.

claim1

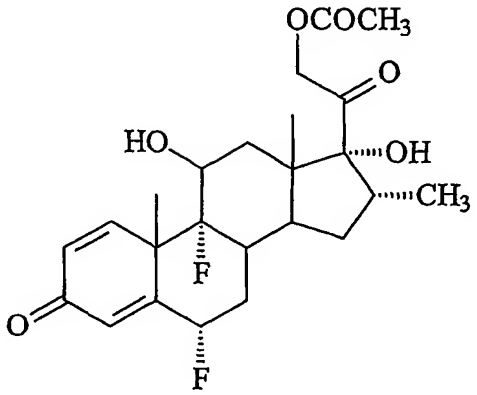
The invention also provides compounds of the formula (V):



(V)

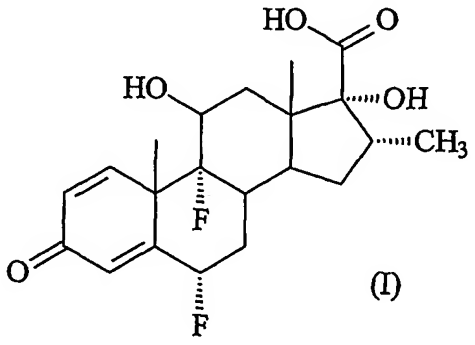
wherein X is hydrogen or fluorine.

In step (d) of the process, the flumethasone 21-acetate formed has the formula:



ie 6a,9a-difluoro-11ß,17a,21-trihydroxy-16a-methyl-pregna-1,4-diene-3,20-dion e,21-acetate. If this compound is hydrolysed, preferably with methanolic potassium hydroxide, the flumethasone free alcohol is formed.

Alternatively, if the flumethasone acetate is hydrolysed, preferably with methanolic potassium hydroxide, and then oxidised, preferably with hydrogen peroxide solution, the so called "hydroxyacid" is obtained, of formula:



(I)

The present invention permits the direct transformation of flumethasone acetate into compound I.

The two new compounds III a) and III b) are depicted as a general formula (V) in claim 8.

The compound I can also be obtained as described in US Patent 3,636,010 by oxidizing flumethasone free alcohol.

The starting material of the present process is commercially available and widely used in the preparation of corticosteroids such as dexamethasone and icomethasone.

In order to introduce fluorine in the C6 position by electrophilic fluorination, it is necessary to activate first the C6 position. For that purpose, the 3-keto group is enolised by carboxylic acid chloride, forming an enolic ester residue of the formula -COR in which R is an aryl or aralkyl group. The preferred compound for the enolisation is benzoyl chloride, yielding the compound of formula III a) in the presence of a tertiary amine, such as pyridine. The preferred solvent is N,N'dimethylacetamide and the reaction is preferably carried out at a temperature of 80 to 85°C, yielding the ?3,5 enol benzoate. Thereafter, the compound III a) is reacted with an electrophilic fluorination agent to yield the corresponding 6 fluoro derivative. The preferred fluorination agent is the 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo [2.2.2]octane bis(tetrafluoroborate), Selectfluor®. So as to realise the fluorination at C6, the preferred solvent is acetonitrile in presence of water at a preferred temperature of -5°C ± 2°C. After the C6 fluorination, the 3 enolic ester can be easily transformed into the system of 3-keto-1,4-diene yielding the compound IV. The elimination of the enolic ester is preferably effected by an aqueous solution of sodium metabisulfite and ammonia.

In the next step, a 9,11-epoxy group of compound IV is reacted with a concentrated aqueous solution of hydrofluoric acid or with a solution of hydrogen fluoride in N,N'dimethylformamide by *per se* known processes at a temperature below 25°C. When compound IV is practically completely reacted, the reaction mixture is poured into a mixture of ice and ammonia sufficient to neutralise the hydrofluoric acid and precipitate simultaneously the flumethasone 21-acetate with a high yield and purity. The product obtained can be recrystallized for instance from methanol. The 21-acetate obtained can be subsequently hydrolyzed by any of the known processes yielding

flumethasone free alcohol. One of the preferred processes is effected in degassed methanolic potassium hydroxide at a temperature between -15°C and -5°C. The end of the reaction is ascertained by HPLC after one hour and it is considered complete when the amount of starting compound is less than 1 %.

In order to carry out the degradative oxidation, according to prior art, flumethasone is suspended in tetrahydrofuran and a solution of the oxidation agent is added dropwise. The substrate first starts to dissolve followed by precipitation. The oxidation is performed preferably at 20°C employing, for example, periodic acid. After one hour of stirring, completion of the reaction is controlled by HPLC. Once the amount of non reacted flumethasone is less than to 0.3%, the reaction is considered complete. Subsequently, the reaction mixture containing compound I is precipitated by adding to an aqueous solution of sodium metabisulfite and ice.

According to the present invention, flumethasone 21-acetate can be simultaneously deacetylated and oxidised by methanolic potassium hydroxide and aqueous hydrogen peroxide yielding, after completion of the reaction, the desired hydroxyacid, compound 1, by acidifying the reaction mixture with diluted hydrochloric acid to pH 2. This reaction is performed at 10°C, ± 2°C with agitation until the reaction is complete.

The cumulative stoichiometric yield of the process described in EP 0610138 B1 so as to obtain unrecrystallized compound I is 48.9% as from 9,11ß-epoxy-17a,21-dihydroxy-pregna-1,4-diene-3,20-dione, whilst according to the present process the cumulative stoichiometric yield obtained is 62.4%, as per Examples 1 b), 2 and 4, as from the 21-acetate of the above starting material. So as to obtain a valid comparison of yields, the starting material of EP 0610138B1 has been first acetylated with a yield of 110% w/w and the cumulative stoichiometric yield was calculated on basis of this value and of Examples 1 b), 2 and 4, resulting in 61.7%.

The following Examples serve to illustrate the present invention without limiting its scope.

EXAMPLE I

9,11ß-epoxy-6a-fluor-17a,21-dihydroxy-16a-methyl-pregna-1,4-diene-3,20-dione, 21-acetate (Formula IV)

a) One dissolves in an inert atmosphere 50 g of 9,11ß-epoxy-17a,21-dihydroxy-16a-methyl pregna-1,4-diene-3,20-dione, 21-acetate in 25 ml of dimethylacetamide (DMA). One adds 65 ml of pyridine and heats the reaction mixture is heated with stirring to between 80°C and 85°C.

Subsequently one adds 33 ml of benzoyl chloride, protected from light, and continues to stir during two to three hours at this temperature and cools it down to 40°c when the reaction is completed. Subsequently, one adds 75 ml of methanol and continues stirring at 40°C for another 30 minutes followed by cooling down the reaction mixture to 20-25°C. Subsequently, one adds the reaction mixture to 1,000 ml of water containing 57.5 ml of hydrochloric acid and 100 ml of dichloromethane. After the extraction, one separates the phases and the aqueous phase is again extracted by an additional 100 ml of dichloromethane. Subsequently, the organic phase is washed with water and with an aqueous solution of sodium hydroxide. The dichloromethane solution thus obtained is evaporated in vacuum to dryness yielding an oil, 3-benzoyloxy-9,11ß-epoxy-17,21-dihydroxy-16a-methyl-pregna 1,3;5-triene-20-one 21-acetate (Formula III a), which is taken up by 150 ml of acetonitrile cooled down to between -5°C and 0°C. Subsequently, one adds the solution of enolbenzoate to a suspension of 44.5 g of 1-chloromethyl-4-fluoro-1,4diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) Selectfluor®, in 175 ml of acetonitrile containing 5 ml of water.

Once the fluorination reaction is completed at C6 (Formula III b), the reaction mixture is poured into a solution of 100 ml water, 1.2 g of sodium metabisulfite, 5 ml of ammonia 25% and 200 ml of dichloromethane. The pH of the solution is adjusted to between 7-8 and is stirred for 30 minutes after which the phases are separated and the organic phase is washed with ammonia 12.5%. Subsequently, the organic phase is evaporated in vacuum until dryness and substituted by

methanol. The desired compound crystallizes, is then filtered and dried at 40 to 45°C, yielding 40 g of the title product with a purity by HPLC of 90%, in area.

b) One repeats Example 1a), but omitting the extraction of the 3-enol benzoate formed, and adding slowly and directly to the reaction mixture 44.5 g of Selectfluor® crystals in four portions. When the content of the starting material is less than 1%, the reaction mixture is poured into 100ml of water containing 1.2g of sodium metabisulfite. The pH is then adjusted to between 7 and 7.5, the solution is stirred for 30 minutes, and the precipitate is filtered and washed. Subsequently, the product thus obtained is washed by suspending it in 150ml of methanol with stirring. After stirring for 30 minutes, it is filtered and dried at a temperature between 40°-45°C, yielding 46 g of 9,11ß-epoxy-6a-fluoro-17a,21-dihydroxy-1,4diene-3,20-dione,21-acetate with a purity of 91.6%.

EXAMPLE 2

6a,9a-difluoro-11ß,17a,21-dihydroxy-16a-methyl-pregna-1,4-diene-3,20-dione,21 acetate (Flumethasone acetate). 36 g of the compound obtained in Example 1 is dissolved in an inert atmosphere in 360 ml of a complex of hydrogen fluoride and dimethylformamide (~64% w/w) at a temperature of 20°C ± 3°. After stirring for three hours at this temperature, it is poured, under agitation, into a mixture of 3,000ml of water, 1,000ml of ice and 800 ml of ammonia 25% maintaining the temperature below 25°C during the whole precipitation. One adjusts the pH to between 4.5 to 5 with ammonia and continues the agitation for one more hour. Subsequently, the precipitate is filtered and washed with water until neutral pH. After drying the compound is dissolved in a mixture of 333 ml of dichloromethane and 148 ml of methanol.

The solution is concentrated until one reaches a volume of 89 ml. The desired product crystallizes. After filtration, it is dried at between 40 to 45°C, yielding 29.2 g of 6a,9a-difluoro-11ß,17a,21-trihydroxy-16a-methyl-pregna-1,4-diene-3,20-dione-3,21-acetate with a purity of 95% by HPLC, in area.

EXAMPLE 3

6a,9a-difluoro-11ß,17a,21-trihydroxy-16a-methyl-pregna-1,4-diene-3,20-dione (Flumethasone)

1.4 g of potassium hydroxide is dissolved in 140 ml of degassed methanol in an inert atmosphere and the solution is cooled to between 0°C and -5°C. Subsequently, the solution is added under stirring to a suspension of 28 g of the compound obtained in the previous example, in 700 ml of degassed methanol. It is stirred during 1 to 2 hours at a temperature of -10°C ± 2°C. Once the reaction is completed, determined by HPLC, one adds acetic acid until pH 7. Subsequently the volume is reduced under vacuum to ~224 ml. Then it is cooled to 10°C and 140 ml of cold water is added. After stirring for one hour at a temperature of between 5°C to 10°C, the compound is filtered, washed with water and dried at 45°C, yielding 22.4 g of the title compound with a purity of 96% by HPLC in area.

EXAMPLE 4

6a,9a-difluoro-11ß,17a-dihydroxy-16a-methyl-17ß-carboxy-androsta-1,4-diene-3-one (Formula I, "hydroxyacid")

2 g of potassium hydroxide is dissolved in a mixture of 100 ml of methanol and 100 ml of water in an inert atmosphere. Subsequently, one adds 10 ml of an aqueous hydrogen peroxide solution (130 vol.) and then cools the reaction mixture to 10°C ± 2°C and one adds 5 g of flumethasone 21-acetate. One stirs overnight at this temperature and once the reaction is completed one adjusts it to pH 2 with hydrochloric acid. Subsequently, it is filtered and washed with water until neutral pH and dried at 45°C. The yield in the title compound is 80% w/w, corresponding to a stoichiometric yield of 91.3%.

EXAMPLE 5

6a,9a-difluoro-11ß, 17a-dihydroxy-16a-methyl-17ß-carboxy-androsta-1,4-diene-3-one.

22 g of flumethasone free alcohol obtained in Example 3 is suspended in 110 ml

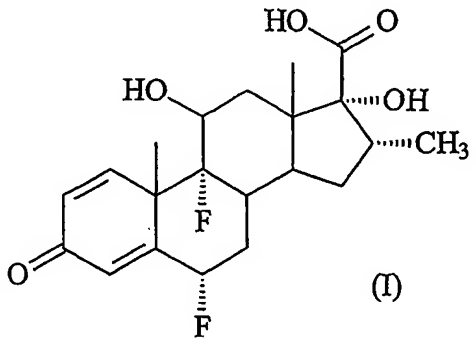
of tetrahydrofurane in an inert atmosphere and is cooled to 20°C ± 2°C. 17.6 g of periodic acid in 70 ml of water is slowly added under stirring. After agitation at the same temperature, one controls the end of the reaction by HPLC, which is generally complete after two hours. Subsequently, the reaction mixture is poured into a solution of 33 g of sodium metabisulfite in 770 ml of water and 330 ml of ice. The product precipitates, is filtered and washed with water until a neutral pH and is dried at 40°C to 45°C, yielding 21 g of the title compound with a purity of 96% in area determined by HPLC.

After recrystallizing the compound thus obtained in ethanol, one obtains 6a,9a-difluoro-11ß,17a-dihydroxy-16a-methyl-17ß-carboxy-androsta-1,4-diene-3-one in high purity having the following analytical values

- optical rotation = +64.4° (c=1 %DMF)
- KF - 0.09%
- Purity by HPLC = 99.2% in area
- Principal absorption peaks in infrared at 1698cm^{-1} -1660cm^{-1} and 1614cm^{-1} - 1603cm^{-1} .

CLAIMS

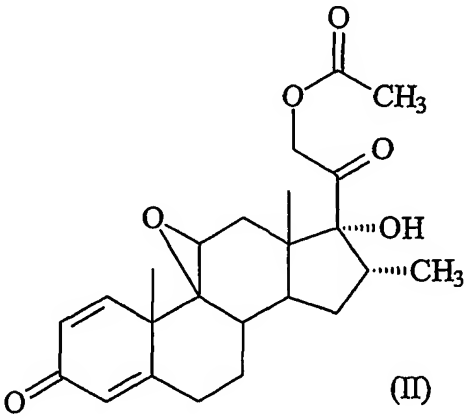
1 A process for preparing flumethasone (6a,9a-difluoro-11ß,17a,21-trihydroxy-16a-methyl-pregna-1,4-diene-3,20-dione), fulmethasone 21-acetate or its 17-carboxyl androsten analogue of the formula:



(I)

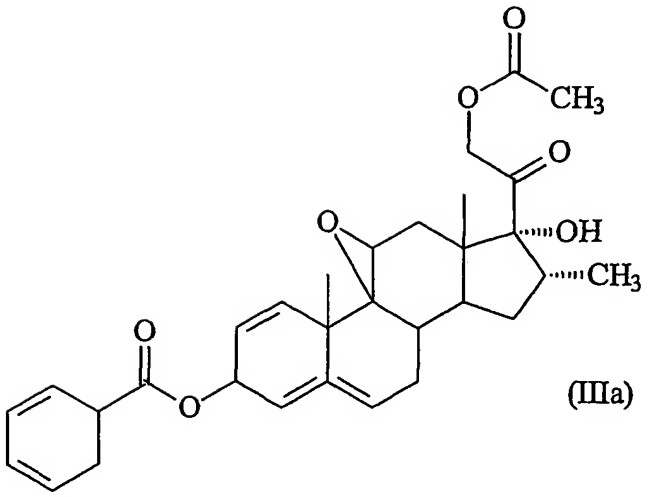
which process comprises

(a) reacting a compound of formula (II)



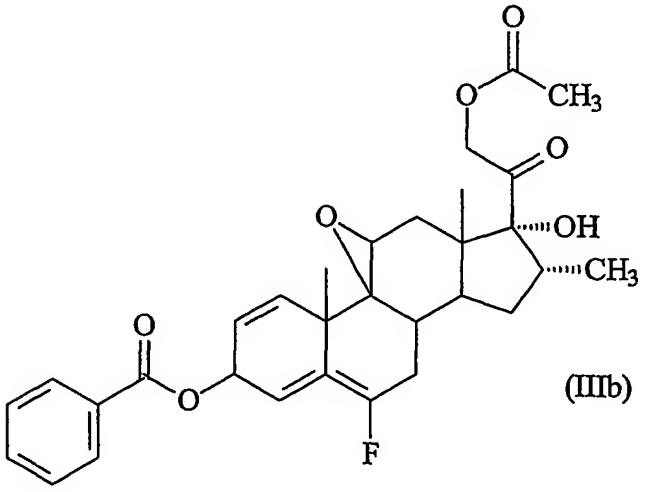
(II)

with benzoyl chloride to form a 3-enolic ester of the formula (IIIa):



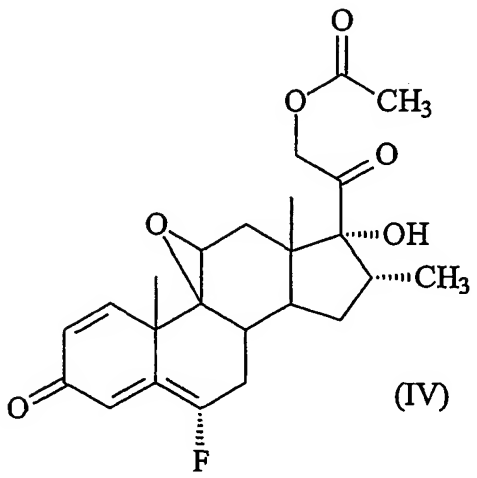
(IIIa)

b) reacting the enol benzoate (III a) with an electrophilic fluorination agent to introduce fluorine in the 6a- position to form a compound of formula (IIIb):



(IIIb)

(c) deprotecting the compound (IIIb) at C3 to form a compound of formula (IV):



(IV)

(d) fluorinating the 9,11-epoxy group of compound IV by reacting it with hydrofluoric acid to yield flumethasone 21-acetate; and optionally

(e) hydrolysing the flumethasone 21-acetate, in the presence or absence of an oxidation agent, to yield compound (I) or flumethasone, respectively.

2 A process according to claim 1 wherein, in step (e), the flumethasone 21-acetate is hydrolysed with methanolic potassium hydroxide.

3 A process according to claim 1 or 2, wherein in step (e) the oxidation agent is aqueous hydrogen peroxide solution.

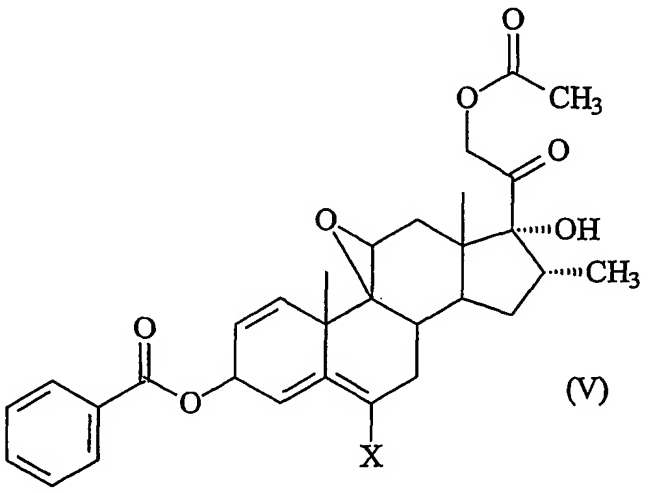
4 A process according to claim 1, 2 or 3, wherein the electrophilic fluorination agent is 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate).

5 A process according to any of claims 1 to 4, wherein in step (c) the deprotection in position C3 is effected using an aqueous solution of metabisulfite and ammonia.

6 A process according to any preceding claim, wherein in step (a) the reaction medium is N,N'-dimethylacetamide and pyridine; and in step (b) the reaction medium is acetonitrile in the presence of water.

7 A process according to any of claims 1 to 6, wherein the reaction temperature in step (a) is from 80 to 85°C and in step (b) is -5° ± 2°C.

8 A compound of the formula (V):



(V)

wherein X is hydrogen or fluorine.

INTERNATIONAL SEARCH REPORT

! ational Application No
PCT/GB 02/02644

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07J5/00 C07J3/00 C07J71/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 610 138 A (ROUSSEL UCLAF) 10 August 1994 (1994-08-10) cited in the application page 6-7	1-8
Y	US 4 188 322 A (CASTELLI PIER P ET AL) 12 February 1980 (1980-02-12) example 3	1-8
Y	US 4 255 331 A (MACDONALD PETER) 10 March 1981 (1981-03-10) column 5, line 33 - line 48 column 2, line 29-34	1-8
Y,P	EP 1 207 166 A (FARMABIOS S R L) 22 May 2002 (2002-05-22) page 3	1-8

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
29 July 2002	10/09/2002

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/02644

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE FILE REGISTRY 'Online! Chemical abstracts (STN); XP002207533 RN: 182202-37-5; Pregna-1,3,5-trien-20-one, 21-(acetyloxy)-3-(benzoyloxy)-9,11-epoxy-1 7-hydroxy-16-methyl-,(9-beta,11-beta,16-be ta) ----	8

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 02/02644

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 0610138	A	10-08-1994	FR	2701262 A1	12-08-1994
			AT	140925 T	15-08-1996
			AU	671695 B2	05-09-1996
			AU	5489294 A	11-08-1994
			CA	2115015 A1	06-08-1994
			CN	1099758 A ,B	08-03-1995
			DE	69400343 D1	05-09-1996
			DE	69400343 T2	16-01-1997
			DK	610138 T3	07-10-1996
			EP	0610138 A1	10-08-1994
			ES	2091100 T3	16-10-1996
			GR	3020750 T3	30-11-1996
			HU	67405 A2	28-04-1995
			HU	69410 A2	28-09-1995
			JP	6279485 A	04-10-1994
			MX	9400910 A1	31-08-1994
			RU	2127739 C1	20-03-1999
			US	5478957 A	26-12-1995
			US	5556965 A	17-09-1996
			ZA	9400778 A	06-02-1995
US 4188322	A	12-02-1980	AT	367772 B	26-07-1982
			AT	311179 A	15-12-1981
			AU	518893 B2	22-10-1981
			AU	4645579 A	01-11-1979
			BE	875939 A1	16-08-1979
			CA	1159049 A1	20-12-1983
			CH	639981 A5	15-12-1983
			DE	2916889 A1	08-11-1979
			DK	173379 A	29-10-1979
			ES	479974 A1	01-09-1980
			ES	8800259 A3	01-01-1988
			FR	2424286 A1	23-11-1979
			GB	2019848 A ,B	07-11-1979
			GR	65300 A1	01-08-1980
			HU	180678 B	29-04-1983
			IE	48329 B1	12-12-1984
			JP	1228571 C	19-09-1984
			JP	54157554 A	12-12-1979
			JP	59001720 B	13-01-1984
			MX	6625 E	04-09-1985
			NL	7903413 A ,B,	30-10-1979
			NO	791440 A ,B,	30-10-1979
			PL	215209 A1	28-01-1980
			PT	69558 A	01-05-1979
			SE	433083 B	07-05-1984
			SE	7903713 A	29-10-1979
			SU	993823 A3	30-01-1983
			ZA	7901977 A	25-06-1980
US 4255331	A	10-03-1981	NL	7902333 A ,B,	09-10-1979
			BE	875327 A2	05-10-1979
			CH	639655 A5	30-11-1983
			DE	2913147 A1	18-10-1979
			FI	791124 A ,B,	06-10-1979
			FR	2421914 A1	02-11-1979
			GB	2018258 A ,B	17-10-1979
			JP	1593737 C	14-12-1990

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 02/02644

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4255331 A		JP 55047700 A	04-04-1980
		JP 63063555 B	07-12-1988
		JP 1025793 A	27-01-1989
		JP 1593847 C	14-12-1990
		JP 2017560 B	20-04-1990
		PH 16138 A	08-07-1983
		AU 532142 B2	22-09-1983
		AU 4607079 A	25-09-1980
		IT 1207228 B	17-05-1989
		IT 1125437 B	14-05-1986
EP 1207166 A	22-05-2002	EP 1207166 A2	22-05-2002
		JP 2002155098 A	28-05-2002
		US 2002062021 A1	23-05-2002